We Claim:

1. An isolated nucleic acid molecule that encodes a polypeptide having poly(ADP-ribose) glycohydrolase (PARG) activity.

2. The nucleic acid molecule of claim 1, wherein said nucleic acid molecule encodes a PARG enzyme selected from the group consisting of bovine PARG, human PARG, murine PARG and drosophila PARG.

3. The nucleic acid molecule of claim 1, which is of mammalian origin.

4. The nucleic acid molecule of claim 1, which comprises a nucleotide sequence with at least 70% similarity with a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, and SEQ ID NO: 9.

5. The nucleic acid molecule of claim 1, which comprises a nucleotide sequence at least 80% similarity with a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, and SEQ ID NO: 9.

6. The nucleic acid molecule of claim 1, which comprises a nucleotide sequence substantially identical with a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, and SEQ ID NO: 9.

7. The nucleic acid molecule of claim 1, which comprises at least about 1000 nucleotides.

8. The nucleic acid molecule of claim 1 wherein the polypeptide has an amino acid sequence with at least 70% sequence similarity to a sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, and SEQ ID NO: 10.

9. The nucleic acid molecule of claim 1, which comprises a nucleotide with at least about70% sequence similarity to the sequence shown in SEQ ID NO: 3 from about residue 2113 to about residue 3105.

10. The nucleic acid molecule of claim 1, which comprises a nucleotide with at least about70% sequence similarity to the sequence shown in SEQ ID NO: 3 from about residue 1240 to about residue 3105.

11. The nucleic acid molecule of claim 1, which comprises a nucleotide with at least about70% sequence similarity to the sequence shown in SEQ ID NO: 3 from about residue 175 to about residue 3105.

12. The nucleic acid molecule of claim 1 which is selected from the group consisting of DNA, RNA and PNA.

13. A vector comprising a nucleic acid molecule of claim 1.

14. The vector of claim 13 wherein said vector is an expression vector comprising a regulatory sequence operatively linked to an expressed nucleotide sequence at least about 1000 base pairs in length, with a sequence similarity to a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, and SEQ ID NO: 9, and wherein said sequence similarity is at least 70%.

15. The vector of claim 14, wherein said sequence similarity is at least 80%.

16. The vector of claim 14, wherein said expressed nucleotide sequence is substantially identical with a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, and SEQ ID NO: 9.

17. The vector of claim 14, wherein said expressed nucleotide sequence is selected from the group consisting of a human PARG and a murine PARG.

18. The vector of claim 13, wherein said vector is an expression vector selected from the group consisting of an eucaryotic expression vector, a procaryotic expression vector, and a viral expression vector.

19. A virus comprising the viral expression vector of claim 18.

20. An oligonucleotide less than about 1000 residues in length comprising a nucleotide sequence at least 10 residues long, which is complementary to a sequence in any one of SEQ ID NOS: 1, 3, 5, 7 and 9.

21. The oligonucleotide of claim 20, which is a DNA, RNA or PNA oligonucleotide.

22. The oligonucleotide of claim 20 which is an anti-sense oligonucleotide.

23. The oligonucleotide of claim 20 which further comprises a ribozyme activity.

24. A cell transformed with a vector of claim 13.

25. The cell of claim 24, wherein said cell is selected form the group consisting of a bacterial cell, a yeast cell, an insect cell and a mammalian cell.

26. An isolated protein having poly(ADP-ribose) glycohydrolase (PARG) activity comprising an amino acid sequence with at least 70% sequence similarity with a sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, and SEQ ID NO: 10.

27. The protein of claim 26, wherein the amino acid sequence has at least 80% sequence similarity with a sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, and SEQ ID NO: 10.

28. The protein of claim 26, wherein the amino acid sequence is substantially identical with a sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, and SEQ ID NO: 10.

29. The protein of claim 26, which has a molecular weight greater than about 100 kDa.

30. The protein of claim 26 which is selected from the group consisting of a murine PARG, a human PARG, a drosophila PARG, an immunoreactive fragments of murine PARG, an immunoreactive fragments of human PARG, and an immunoreactive fragments of drosophila PARG.

31. An isolated polypeptide with at least 80% sequence similarity with a sequence shown in any one of SEQ ID NOS: 2, 4, 6, 8 and 10.

32. The polypeptide of claim 31, which has a molecular weight less than about 65 kDa and which is at least 6 amino acid residues in length.

33. The polypeptide of claim 31, which has a molecular weight less than about 40 kDa and has at least 90% sequence similarity with a sequence shown in any one of SEQ ID NOS: 2, 4, 6, 8 and 10.

34. The polypeptide of claim 31, which has poly(ADP-ribose) glycohydrolase (PARG) activity.

35. The polypeptide of claim 31, which comprises an amino acid sequence substantially identical with SEQ ID NO: 4 from about residue 647 to about residue 977.

36. A method of preventing, treating, or ameliorating a disease condition in an individual in need thereof comprising administering a therapeutically effective amount of a PARG modulator to the individual.

37. The method of claim 36, wherein the disease state is a neoplastic disorder, a myocardial infarction, a vascular stroke or a neurodegenerative disorder.

38. The method of claim 36, wherein the PARG modulator is an anti-sense oligonucleotide, which hybridizes in-vivo to messenger RNA encoded by a PARG gene.

39. The method of claim 36 wherein the PARG modulator is a vector which expresses an antisense nucleotide message.

40. A method of identifying an agent that modulate poly(ADP-ribose) glycohydrolase (PARG) activity comprising:

(i) providing a liquid medium that contains a polypeptide having PARG activity;

(ii) contacting the polypeptide with a candidate agent, in the presence of a reference compound having affinity for the polypeptide, under predetermined assay conditions; and

(iii) determining the affinity of the candidate agent for the polypeptide relative to the reference compound, thereby determining the modulation activity of the candidate agent relative to the reference compound.

41. A method of identifying a mutant PARG allele in an individual comprising:

(i) obtaining genomic material from the individual;

(ii) digesting the genomic material with a restriction enzyme having a recognition site inclusive of said mutant allele;

(iii) fractionating the restriction fragments obtained from said digestion; and

(iv) comparing the fractionation pattern with that obtained for a normal allele, thereby determining the presence or absence of the mutant allele.

42. The method of claim 41, wherein said fractionation is performed with electrophoresis.

43. A method of screening candidate molecules for PARG modulating activity, comprising the steps of:
providing a purified PARG enzyme;
assaying the enzyme in the presence of a candidate molecule to be screened; and
comparing the activity of the PARG enzyme in the presence of the molecule to the activity of the PARG enzyme in the absence of the molecule.

44. A method for gene therapy comprising the step of delivering to a cell to be treated an oligonucleotide having a sequence complementary to at least a portion of a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, and SEQ ID NO: 9.

45. The method of claim 44 wherein the oligonucleotide has a sequence complementary to a sequence encoding a C-terminal portion of a PARG enzyme.

46. The method of claim 44, wherein the oligonucleotide is an RNA and further comprises a ribozyme.

47. A method of sensitizing a cell to a chemotherapeutic agent, comprising the step of contacting the cell with a molecule that modulates an enzymatic activity of a PARG enzyme.

48. The method of claim 47, wherein the molecule is an oligonucleotide having a sequence complementary to at least a portion of a polynucleotide encoding a PARG enzyme.

49. The method of claim 47, wherein the oligonucleotide has a sequence complementary to a sequence encoding a C-terminal portion of a PARG enzyme.

50. The method of claim 47, wherein the oligonucleotide further comprises a ribozyme.

51. A method of treating a diseased cell characterized by the presence of DNA strand breaks, comprising the step of contacting the cell with a molecule that modulates an enzymatic activity of a PARG enzyme.

52. The method of claim 51, wherein the molecule is an oligonucleotide having a sequence complementary to at least a portion of a polynucleotide encoding a PARG enzyme.

53. The method of claim 51, wherein the oligonucleotide has a sequence complementary to a sequence encoding a C-terminal portion of a PARG enzyme.

54. The method of claim 51, wherein the oligonucleotide further comprises a ribozyme.

55. An antibody that is specifically immunoreactive with the polypeptide of claim 1.

56. The antibody of claim 55 selected from the group consisting of antibodies, antibody fragments, Fc fragments, Fab fragments, Fab' fragments, and Fab'(2) fragments.

57. The antibody compound of claim 55, wherein the antibody binds to an N-terminal portion of a PARG enzyme.

58. The antibody-like compound of claim 55, wherein the antibody binds to a C-terminal portion of a PARG enzyme.

59. A pharmaceutical composition comprising an nucleic acid molecule having a sequence complementary to at least a portion of a polynucleotide encoding a PARG enzyme.

60. The pharmaceutical composition of claim 59, wherein the oligonucleotide has a sequence complementary to a sequence encoding a C-terminal portion of a PARG enzyme.

61. The pharmaceutical composition of claim 59, wherein the oligonucleotide further comprises a ribozyme.

62. A transgenic knockout mouse comprising a homozygous disruption in its endogenous PARG gene, wherein said disruption prevents the expression of a PARG protein, and further wherein the phenotype of said knockout mouse relative to a mouse having a wild type PARG gene comprises:
an absence of PARG activity.

63. The knockout mouse of claim 62, wherein the disruption comprises an insertion into a coding region of the PARG gene.

64. The knockout mouse of claim 62, wherein the insertion replaces DNA at the start of the coding region of the PARG gene.

65. A nucleic acid molecule which encodes a polypeptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, and SEQ ID NO: 10.

66. A nucleic acid molecule which hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, and SEQ ID NO: 9.